

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH**

SUMMARY OF TOXICOLOGY DATA

ZOXAMIDE (also designated as RH-117,281 Technical or RH-7281 Technical)

Chemical Code # 5769 Tolerance # 52861

SB 950 # N/A

Original date: 6/6/01

Revised date: 6/12/01

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time †

Toxicology one-liners are attached.

† There are acceptable rat acute and subchronic neurotoxicity studies with negative results.

All record numbers through 178576 (Document No. 52861-052) were examined. This includes all records indexed by DPR as of 6/6/01.

In the one-liners below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: t186545.doc

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****52861-036 178559** Ivett, J. L., "RH-117,281 Technical: 24-month dietary chronic/oncogenicity study in rats," Covance Laboratories Inc., 11/3/98. Sponsor Study ID: R&H 94RC-236. Sixty CrI:CD®BR rats/sex/group were treated for up to 2 years in diet with 0, 1000, 5000, or 20000 ppm Zoxamide (RH-117,281 Technical, purity 92.0 %) in a guideline rat combined chronic/oncogenicity study. An additional 10/sex/group were designated as 1-year interim sacrifice rats. Dietary levels were adjusted to 100 % a.i. There were no definitive treatment effects at any dose, hence NOEL = 20000 ppm: a "limit dose" [estimated dose of 1058 mg/kg/day in males and 1331 mg/kg/day in females]. **Acceptable, with no adverse effects.** Aldous, 3/7/01.

52861-037 178560 Selection of representative slides for record 52861-036 178559, above. Twenty slides were provided, all at 160X. One rat/sex/group was examined in control and high dose rats in five tissues. Slides were not chosen to represent unusual findings. **Supplemental** data to the primary study. No worksheet. Aldous, 3/16/01.

CHRONIC TOXICITY, DOG

****52861-035 178558** Ferguson, J. S., R. D. Morrison, and B. F. Davidson, "RH-7281 Technical: one-year chronic dietary toxicity study in dogs," Rohm and Haas Company, Springhouse, PA, 6/9/98. Report No. 95R-277. Four beagle dogs/sex/group were dosed in diet with Zoxamide (RH-7281 Technical, 92.3% purity) for 1 year at 0, 1500, 7500, and 30000 ppm [estimated dose levels of 0, 50, 255, and 1016 mg/kg/day (M), and 0, 48, 278, and 994 mg/kg/day (F), respectively]. NOEL = not defined (one 1500 ppm male had apparent canine juvenile polyarteritis syndrome, considered to be a treatment response in pre-disposed dogs). A "NOEL" excluding that syndrome, based upon reduced body weight gain and increased relative liver weight, is 1500 ppm in females and 7500 ppm in males. Findings at 30000 ppm included reduced food consumption and reduced body weight gain, liver weight increases, liver hepatocellular hypertrophy, clinical chemistry changes consistent with liver pathology (elevated alkaline phosphatase, reduced albumin), and increased relative thyroid weights (the latter in females only). Also, one high dose female was euthanized after suffering from apparent canine juvenile polyarteritis syndrome (beagle pain syndrome), a rare disease which appears to be immune-mediated, and is associated with marked inflammation in various tissues. Since an additional treated dog (low dose male) also had histopathologic evidence of the disease (although the male was asymptomatic), investigators considered it plausible that the symptoms may have reflected a treatment response in predisposed dogs. Investigators considered the findings to be not relevant to human health because the responses are species-specific and to a large extent characteristic of a particular breed of dogs (beagles). Since the concurrent 3-month dog subchronic study (Record No. 178536) also found evidence of this polyarteritis syndrome, these results identify a **"possible adverse effect."**

Interpretation of this endpoint should consider the low incidence, lack of dose-response, the high dose range tested, and species/strain specificity of this finding. Study is **acceptable** with some deficiencies as noted in the review. Aldous, 4/25/01.

ONCOGENICITY, MOUSE

****52861-038 178561** Robison, P., D. M. Anderson, and B. F. Ecke, "RH-117,281 Technical: Eighteen-month dietary oncogenicity study in mice," Rohm and Haas Company Toxicology Department, Spring House, PA, 11/6/98. Report ID: Rohm and Haas 96R-094. Sixty Crl:CD-1 (ICR) BR (VAF/+) mice/sex/group were dosed in diet with 0, 350, 1750, or 7000 ppm zoxamide (RH-117,281 Technical, 92.3% a.i., doses adjusted for purity) for 78 weeks in a guideline-design oncogenicity study. Estimated achieved mean dosages were 51, 251, and 1021 mg/kg/day for males, and 60, 326, and 1289 mg/kg/day for females. Chronic NOEL = 7000 ppm. Transitory, minor body weight decrements in high dose males suggest a "subacute NOEL" of 1750 ppm in males. There were no short-range effects in females. **Acceptable, with no adverse effects.** Aldous, 6/1/01.

52861-040 178563 Robison, Patricia [Report Supplement No. 96R-094C], "Historical control data: body weights, convulsions in the CD-1 mouse and spontaneous neoplastic lesions", report supplement date: 7/21/99. Data were produced in response to a request by a reviewing U. S. EPA toxicologist with reference to study 96R-094 (DPR designations 52861-038 178561, above). Appendix 1 presented body weight data from the testing facility and from outside facilities for both sexes, showing that body weights observed in the cited oncogenicity study were typical for the strain. Appendix 2 is a letter by H. Rozmiarek, D.V.M., Ph.D., in which he characterized spontaneous seizure activity in otherwise normal CD-1 mice. Typical pattern in these mice is body stiffening, vocalization, arching of the head, salivation, whole body clonic and tonic convulsions, and opisthotonus. This activity usually occurs during palpation or follows immediately thereafter, and the mouse is typically back to normal behaviors by 5-10 seconds. Incidence rates in three different facilities ranged from 22% to 34%, with an average of 6 seizures per affected mouse over a period of 63 weeks. No evidence of ongoing disease processes has been identified: it appears that the convulsions are a feature of the strain. Appendix 3 is a copy of the Charles River Laboratories report of "Spontaneous neoplastic lesions in the Crl:CD-1® BR mouse", dated March, 1995. None of these data had been solicited by DPR, and the study had been accepted by DPR upon initial review, hence no worksheet is needed. Aldous, 5/11/01.

52861-039 178562 Gillette, D. M. and W. R. Brown, [Report Supplement No. 96R-094A], report supplement date: 9/24/98. Data were produced in support of study 96R-094 (DPR designations 52861-038 178561, above). This report contains photomicrographs of several normal mouse tissues from the cited study. No worksheet. Aldous, 5/11/01.

REPRODUCTION, RAT

****52861-043 178566** O'Hara, G. P., L. P. Craig, and A. S. Romanello, "RH-117,281

Technical: Two-generation toxicity study in rats”, Rohm and Haas, Spring House, PA, 12/10/98. Report No. 95R-272. CrI:CD@BR rats, 30/sex/group, were dosed in diet with Zoxamide (RH-117,281 Technical), 92.3% purity in diet at 0, 1000, 5000, or 20000 ppm for 2 generations, with 2 littering periods per generation. In response to findings in weanlings in F1a to F2a littering periods, investigators altered the exposure regimen for the F2b period so that all P2 dams and half of the litters/treatment were dosed by gavage during days 14-21 post-partum with 0, 50, 250, or 1000 mg/kg/day in 5 ml/kg b.w. of corn oil vehicle instead of respective diets. Study design followed EPA guidelines, and included (1) assessments of estrous stage of females by vaginal lavage during the final three weeks of respective pre-mating periods, (2) rats selected to be P2 parents were evaluated for indices of sexual maturation (preputial separation or vaginal patency), and (3) all P1 and P2 males were evaluated for epididymal sperm motility, sperm morphology, sperm count, and sperm concentration; also testicular spermatid counts were recorded. Reproductive NOEL = 20000 ppm (M: 1474-2091 mg/kg/day; F: 1624-2239 mg/kg/day, based on effects on reproductive indices). A NOEL of 50 mg/kg/day (gavage exposure to dams and pups during days 14-21 of the F2b littering period) is below the exposure associated with meaningful changes in any stage of life evaluated in this study. At the lowest dose tested with dietary exposure, the findings were (1) significantly reduced pup weights at lactation day 21 (but not at day 14), and (2) significantly reduced spleen weights associated with decreased extramedullary hematopoiesis in splenic red pulp. Approximate exposure to the low dose (1000 ppm) weanling pups was probably near to recorded compound intake for 1000 ppm P2 adults during the first week of the pre-mating period (239 mg/kg/day in M and 221 mg/kg/day in F). A NOEL strictly for parental rats (excluding reduced body weight in 1000 ppm pups during the first week of the P2 pre-mating growth period) is 1000 ppm (71 mg/kg/day, based on P1 male pre-mating phase intake), indicated by increased relative liver weights in M and F P1 parents, and on modest body weight decrements of P2 dams at terminal sacrifice. Study is **acceptable, with no adverse effects**. Aldous, 6/1/01.

TERATOLOGY, RAT

52861-041 178564 Kane, W. W. and D. L. Shuey, “RH-7281 Technical: oral (gavage) developmental toxicity study in rats,” Rohm and Haas, Spring House, PA, 9/15/94 . Report No. 94R-079. Groups of 25 CrI:CD@ BR dams were dosed by gavage in corn oil (10 ml/kg) at 0, 100, 300, or 1000 mg/kg/day Zoxamide (RH-7281 Technical, 94.2% a.i.) on days 6-15 of gestation in a guideline developmental study. Maternal and developmental NOEL = 1000 mg/kg/day (highest dose tested). The study is **acceptable, with no adverse effects. Aldous, 4/30/01.

TERATOLOGY, RABBIT

52861-042 178565 Shuey, D. L., “RH-117,281 Technical: oral (gavage) developmental toxicity study in rabbits”, Rohm and Haas, Spring House, PA, 4/8/97. Report No. 95R-267. Sixteen mated New Zealand White rabbits/group were dosed by gavage during gestation days 7-19 with 0, 100, 300, or 1000 mg/kg/day Zoxamide (RH-117,281 Technical, 92.3 % a.i.) in 0.5% aqueous methylcellulose, 20 ml/kg body weight. Maternal and developmental NOEL = 1000 mg/kg/day (highest dose tested). Study is **acceptable, with no adverse effects. Aldous, 4/30/01.

GENE MUTATION

****52861-044 178567** Sames, J. L. and P. J. Ciaccio, “RH-117,281 Technical: *Salmonella typhimurium* gene mutation assay”, Rohm and Haas, Spring House, PA, 10/25/96. Report No. 95R-262. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were tested initially with 0, 50, 200, 500, 2000, and 5000 µg/plate (6 reps/dose) with and without S-9 activation. The first assay determined that in most cases, dose levels at or above 500 µg/plate with S-9 or 200 µg/plate without S-9 caused precipitates. As a result, the confirmatory assay utilized reduced treatment ranges with maximum dose levels of 160 µg/plate without S-9 and 300 µg/plate with S-9. Generally in the latter assay, only the highest levels had precipitation. Results were negative at all dose levels tested. Positive controls were functional. **Acceptable, with no adverse effects.** Aldous, 6/1/01.

****52861-046 178570** Pant, K. J., “Test for chemical induction of gene mutation at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells with and without metabolic activation”, SITEK Research Laboratories, Rockville, MD, 11/16/94. Report No. 94RC-077. CHO cell line (CHO-K1), clone CHO-K1-BH4 was evaluated for forward mutations in two independent assays, with paired cultures treated at each dose level with and without S-9 activation. There were functional positive controls for each case. The study is **acceptable** with some deficiencies as noted in the DPR review. **No adverse effect.** Aldous, 6/1/01.

CHROMOSOME EFFECTS

****52861-047 178571** Riley, S., “RH-117,281: test for chemical induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells”, Covance Laboratories Inc. (Harrogate, North Yorkshire, England), Dec. 1998. Report No. 96RC-125. RH-117,281 (Zoxamide), purity 92.3%, was applied to CHO cells for 3 hr with S-9 (+ 17 hr recovery) or 20 hr without S-9 in a standard chromosomal aberration assay. Duplicate cultures were tested at each treatment level. There were two independent experiments. The second experiment included a test using 3 hr with S-9 (+ 41 hr recovery) or 44 hr without S-9, in addition to the 20-hr assays noted above. In all cases, colchicine was added 1.5 hr before harvest. Three treatment groups were employed per experiment. Generally the selected high dose level reduced relative cell growth (compared to solvent control) by at least 50%. Positive controls were functional. There were no consistent increases in structural aberrations. Numerical aberrations (principally polyploidy) were profoundly increased at the higher dose levels in the second experiment subgroups with extended incubation times, with and without S-9. Numerical aberrations were elevated to a lesser extent in trial 1 without S-9. Numerical aberration increases constitute a “**possible adverse effect**” of unknown biological importance. **Acceptable.** Aldous, 6/1/01.

DNA DAMAGE

****52861-048 178572** Sames, J. L. and Y. L. Vandenberghe, “RH-117,281 Technical:

micronucleus assay in CD-1 mouse bone marrow cells”, Rohm and Haas, Spring House, PA, 10/29/96. Report No. 95R-264. At least 5 mice/sex/dose received 0, 200, 1000, or 2000 mg/kg zoxamide (purity 92.3%) by gavage (corn oil, single treatment) at each of two pre-sacrifice intervals: 24 hr or 48 hr. Positive controls (5/sex at each of two dose levels: 0.35 and 2.0 mg/kg) were dosed ip with mitomycin C in distilled water 24 hr before sacrifice. There were no deaths, and no toxicity attributable to zoxamide. Some anogenital yellow staining and some diarrhea appeared to be due to corn oil, but was limited to the day of dosing. There was no pattern of PCE/NCE ratios suggestive of cytotoxicity. There was no treatment-related increase in micronuclei. Positive controls were functional. Study is **acceptable, with no adverse effects**. Aldous, 5/14/01.

52861-049 178573 Swenson, R. E. and C. B. Frederick, [supplemental data relating to Report No. 95R-264 (mouse bone marrow micronucleus assay), DPR Document No. 52861-048 and Record No. 178572]. “Distribution of ^{14}C -RH-117,281 to the bone marrow of mice”, Rohm and Haas, Spring House, PA, 7/24/98. Report No. for this supplement: 97R-173. Groups of 4 CD-1 mice/sex, fasted for 3 hr before dosing, were administered 2000 mg/kg zoxamide [labeled zoxamide was 99.5% radiopurity, unlabeled zoxamide was 92.3% a.i.] by gavage in corn oil at 4 hr, 8 hr, 24 hr, or 48 hr before sacrifice. Bone marrow and whole blood samples were evaluated for radiolabel at all time periods. Results were expressed in $\mu\text{g }^{14}\text{C}$ equivalents/g tissue. At 4 hr, marrow and blood contained similar equivalents of label/g. By 8 hr, the ratio of equivalents of marrow to blood was about 1:2, and at subsequent intervals the ratio was about 1:3. This study validates that exposure to the bone marrow was sufficiently high to permit a meaningful micronucleus assay. Useful **supplemental** data. Aldous, 6/6/01.

MUTAGENICITY STUDIES USING METABOLITES

52861-045 178568 Sames, J. L. and P. J. Ciaccio, “RH-141,452: *Salmonella typhimurium* gene mutation assay”, Rohm and Haas, Spring House, PA, Oct. 1, 1998. R&H Report No. 98R-050. Test article is a metabolite of zoxamide, of 97.7% purity. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were tested in the definitive study with 0, 50, 200, 500, 2000, and 5000 $\mu\text{g}/\text{plate}$ (in triplicate) with and without S-9 activation. A confirmatory test was performed at the same dose levels. Both tests were negative. Positive controls were functional. Doses up to the limit test were unaffected by cytotoxicity or precipitation. This is a valid **supplemental** study. Aldous, 5/16/01.

52861-045 178569 Sames, J. L. and P. J. Ciaccio, “RH-141,455: *Salmonella typhimurium* gene mutation assay”, Rohm and Haas, Spring House, PA, 9/23/98. R&H Report No. 98R-048. Test article is a metabolite of zoxamide, of 98.7% purity. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 were tested in the definitive study with 0, 50, 200, 500, 2000, and 5000 $\mu\text{g}/\text{plate}$ (in triplicate) with and without S-9 activation. A confirmatory test was performed at the same dose levels. Both tests were negative. Positive controls were functional. Doses up to the limit test were unaffected by precipitation. The 5000 $\mu\text{g}/\text{plate}$ groups and occasionally the 2000 $\mu\text{g}/\text{plate}$ groups had dose-related reductions in mutant colonies compared to solvent controls, particularly evident with TA100 and TA102. This is a valid **supplemental** study. Aldous, 5/16/01.

METABOLISM

52861-050 178574 Swenson, R. E., C. B. Frederick, and D. D. Graves, “[¹⁴C]-RH-117,281: Pharmacokinetic and metabolism study in rats”, Rohm and Haas, Spring House, PA, 10/15/98. Report No. 94R-235. Investigators studied all major elements of a metabolism study in male and female Crl:CD® BR rats, including excretion patterns following a single gavage dose (in corn oil) of 10 mg/kg or a single dose of 1000 mg/kg labeled zoxamide, or single dose of 10 mg/kg labeled zoxamide after 2 weeks of administration of 200 ppm non-labeled zoxamide in diet. Tissue distribution of residues was determined after 8, 22, and 120 hr. Major metabolites were determined in feces, urine, and in bile over a range of time intervals. Blood kinetics were assessed. Exhaled air was evaluated for ¹⁴C content (this was found not to be a significant route). Bile ducts were cannulated to assess degree of biliary excretion and associated metabolites. Investigators isolated 36 compounds including parent zoxamide in urine and/or feces. Bile contained 17 separable components. Major metabolites by each route were identified. Administration of 10 mg/kg zoxamide led to appreciable recovery of unaltered zoxamide in feces (12-23%). Much higher unaltered zoxamide were found in feces (72-74%) following a 1000 mg/kg dose. At least 71% of administered dose was found in feces after 10 mg/kg treatment (with or without dietary pre-treatment). Several metabolic routes were evident from analysis of fecal metabolites, including as initial steps: reductive dehalogenation, hydrolysis to provide an α -keto alcohol, or glutathione conjugation at the chloro group of the side chain. Often the final metabolites were products of subsequent oxidation to provide benzoic acid substituents or oxidation of the side chain to one of several carboxylic acid moieties, depending upon the amount of degradation of the side chain. There was no single dominant urinary metabolite. Most of these had been oxidized to expose several polar groups, and included several glutathione and glucuronide conjugation products. Rats treated with 10 mg/kg [¹⁴C]-RH-117,281 following 2 weeks of administration of 200 ppm non-labeled zoxamide had excretion patterns similar to those of non-pre-treated rats. Biliary metabolites in cannulated rats constituted 46-48% of dose. Various glutathione derivatives predominated in the bile, and some residues underwent hydrolysis or reductive dehalogenation followed by glucuronide formation. Mean plasma radioactivity concentrations peaked at 8 hr following 10 mg/kg or 1000 mg/kg zoxamide, and time of one-half peak concentration was 22 hr. Tissue levels as percentage of administered dose were generally about twice as high in the 10 mg/kg groups compared to high dose rats, consistent with the above evidences of poor absorption at 1000 mg/kg. Only the alimentary tract and liver had remarkably high concentrations at 8 hr, with marked reduction in most tissues by 22 hr after dosing. Thus zoxamide and its metabolites tend not accumulate in the body. There were no remarkable sex differences in zoxamide disposition. **Acceptable, with no adverse effects. Aldous, 6/6/01.

52861-051 178575 Wu, D. and Z. Gu, “[¹⁴C]-RH-141,452: rat metabolism study, tier 1 testing”, Rohm and Haas, Spring House, PA, 11/19/98. Report No. 97RC-154. Four male Crl:CD® BR rats were dosed by gavage in water once at 1000 mg/kg with RH-141,452, (3,5-dichloro-4-hydroxymethyl benzoic acid), a metabolic product of zoxamide. Purity of unlabeled test article was 100%. Radiopurity of ¹⁴C-ring-labeled test article was 98%. Investigators assessed recoveries in urine, feces, and exhaled air, and identified major metabolites in urine and feces. Urinary excretion was about 98% of dose, feces 1.7%, and expired air about 0.01%. Nearly all of urinary excretion was

complete within 24 hr, and most fecal excretion occurred within 48 hr (pp. 96 ff.). About 94% of dose was excreted in urine as the test article (pp. 36-37). Collectively, three minor metabolites accounted for another 3% of urinary label (glucuronides of the hydroxyl or carboxylic acid groups, or glycine conjugate of the carboxylic acid group). Nearly all fecal label represented test article (p. 42). Tissues were not analyzed at 78 hr termination of rats. Useful **supplemental data**. Aldous, 5/22/01.

52861-052 178576 Wu, D. and Z. Gu, “[¹⁴C]- RH-141,455: rat metabolism study, tier 1 testing”, Rohm and Haas, Spring House, PA, 11/19/98. Report No. 98RC-017. Four male Crl:CD® BR rats were dosed by gavage in water once at 1000 mg/kg with ring-labeled [¹⁴C]- RH-141,455 (this is the dicarboxylic acid metabolite of zoxamide). Purity of unlabeled RH-141,455 was 98.77%. Radiopurity of ¹⁴C- RH-141,455 was > 96%. Investigators assayed residues in urine, feces, and exhaled air, and identified major metabolites in urine and feces. Tissues were not analyzed at 168 hr termination of rats, since nearly all label could be found in excreta. Recoveries of radiolabel averaged 75.5% in feces, 11.0% in urine, and 9.3% in cage rinse (p. 27). Due to diarrhea, much of the cage rinse may have represented fecal output (p. 10). About 0.01% of dose was found in expired air. Label recovery in feces, urine, or cage rinse dropped off quickly after the first 48 hr after dosing (pp. 28-30). Parent compound was the only significant peak detected after HPLC separation of extracts of fecal and urinary samples (pp. 38-40). Useful **supplemental data**. Aldous, 6/6/01.

SUBCHRONIC (with or without neurotoxicity component)

(Oral)

52861-031 178535 Morrison, R. D. and D. M. Gillette, “RH-117,281: Three-month dietary/neurotoxicity study in rats,” Rohm and Haas (Spring House, PA), 3/22/96. Report No. 94R-233. Fifteen Crl:CD® BR rats/sex/group were dosed in diet with 0, 1000, 5000, or 20000 ppm (M: 0, 74, 372, 1509 mg/kg/day; F: 0, 80, 401, 1622 mg/kg/day) zoxamide (RH-117,281 Technical) (92.9% a.i., diets adjusted for percent a.i.) for 3 months in a subchronic toxicity and neurotoxicity study. Of each group of 15, ten were utilized for FOB and motor activity evaluations pre-test and at weeks 4, 8, and 13. Five of the latter subgroups were perfusion fixed for evaluation of brain (6 sections), Gasserian ganglia, spinal cord (cervical, thoracic, and lumbar cross sections plus longitudinal sections of the proximal cervical cord), dorsal and ventral root fibers, and dorsal root ganglia. These tissues were embedded in paraffin prior to H&E staining. Peripheral nervous system samples (sciatic, sural, peroneal, and tibial nerves in cross- and longitudinal-sections) were embedded in glycol methacrylate and stained with toluidine blue. The ten rats/sex/group which were not perfusion fixed were processed for routine histopathology. Only controls and high dose rats were examined for histopathology in all cases. This study did not identify treatment effects. NOEL = 20000 ppm (highest dose tested: 1509 mg/kg/day in M: 1622 mg/kg/day in F). **Acceptable. Aldous, 6/1/01.

033; 178537; “RH-117,281 Technical: Acute Oral (Gavage) Neurotoxicity Study in Rats” (Danberry, T.L. and Gillette, D.M., Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. 95R-182, 1/6/97). 818. RH-117,281 Technical (Lot No. LG3517, purity = 92.9%), suspended in corn oil, was administered by gavage in a single dose to 10 Crl:CD® BR rats per sex per dose at dose levels of 0 (vehicle only), 125, 500, and 2000 mg/kg. No mortalities occurred. Red stained muzzle was observed in 3 females on the day of dosing after test article administration (Day 0)

with all signs of red stained muzzle clearing by Day 1. No treatment-related clinical signs were observed in males. No treatment-related effects were observed during FOB evaluations. No treatment-related motor activity effects were observed. Necropsy and microscopic examination of preserved nervous system tissues revealed no treatment-related abnormalities. **No adverse effects.** NOEL (M) = 2000 mg/kg (based on no effects at the highest dose tested). NOEL (F) = 500 mg/kg (based on treatment-related clinical signs). **Acceptable.** (Corlett and Leung, 5/1/01)

030; 178534; "RH-117,281: Three Month Dietary Toxicity Study in Mice" (Shuey, D.L. et al., Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. 94R-075, 2/9/96). RH-117,281 Technical (Lot No. DK2011, purity = 94.2%) was admixed to the diet at dose levels of 0 (diet only), 70, 700, 2500, or 7000 ppm (for males, 0, 12, 123, 436, and 1212 mg/kg/day, respectively, and for females, 0, 17, 174, 574, and 1666 mg/kg/day, respectively) and fed to 10 Crl:CD-1 (ICR) BR VAF/+ mice per sex per dose for 3 months. No animals died. No treatment-related clinical signs were observed. A treatment-related decrease in mean body weight and a treatment-related increase in mean relative liver weight in females at 7000 ppm were observed. Necropsy revealed no treatment-related gross lesions. Microscopic examination of tissues from control and high dose group animals revealed no treatment-related findings. NOEL (M) = 1212 mg/kg (7000 ppm) (based on no effects at the highest dose tested), (F) = 574 mg/kg (2500 ppm) (based on a decrease in mean body weight and an increase in mean relative liver weight). **Supplemental** (no ophthalmologic examinations were conducted on the test animals). (Corlett, 5/3/01)

52861-032 178536 Ferguson, J. S., R. D. Morrison, and M. G. Kemmerer, "RH-7281 Technical: Three-month dietary toxicity study in dogs," Rohm and Haas, Springhouse, PA, 10/8/97. Report No. 96R-030. Four beagle dogs/sex/group were dosed in diet with Zoxamide (RH-7281 Technical, 92.3% purity) for 16 weeks (except that one replacement low dose female was exposed 13 weeks) at 0, 1500, 7500, and 30000 ppm [estimated dose levels of 0, 54, 281, and 1139 mg/kg/day (M), and 0, 62, 322, and 1054 mg/kg/day (F), respectively] in a standard subchronic study. NOEL = 1500 ppm (presumptive canine juvenile polyarteritis syndrome in a mid-dose male, and increased absolute and relative liver weights in mid-dose females). Findings at 30000 ppm included reduced body weights and reduced food consumption (M&F), transitory signs of canine juvenile polyarteritis syndrome in one male and histopathology indicative of the above syndrome in one female at 30000 ppm, modest hematology differences for RBC's [reduced RBC count (M), increased mean cell hemoglobin (M), and increased mean cell hemoglobin concentration (M)], and for WBC differentials [reduced % lymphocytes at day 113 (but not at day 58)], small reduction in albumin concentration (significant only in M), slight increase in adrenal relative weights (M) and significant increases in relative and absolute liver weights (M&F), liver hypertrophy in all high dose dogs, and necrotizing vasculitis in multiple organs in one high dose female (evidence of canine juvenile polyarteritis syndrome). **Acceptable**, with **no adverse effect** (however, see the results of the associated chronic study, which did not achieve a NOEL for the above syndrome). Aldous, 4/26/01.

(Dermal)

034; 178557; "RH-7281: Twenty-Eight Day Dermal Toxicity Study in Rats" (Robison, P. et al., Rohm and Haas Company, Toxicology Department, Spring House, PA, Report No. 97R-075, 10/16/98).

822. RH-7281 Technical (Lot No. R63240, purity = 93.83%), moistened with tap water, was applied to the shaved skin of 10 CrI:CD[®]BR rats per sex per dose at dose levels of 0 (tap water treated only), 150, 400, or 1000 mg/kg/day for 6 hours per day, 5 days a week for 28-30 days using an occlusive wrap. No animals died. No treatment-related signs of systemic toxicity were observed. Scabbed and reddened areas of treated skin at all 3 dose levels were observed throughout the study. No treatment-related body weight, organ weight, hematological, or serum chemistry effects were observed. Macroscopic and microscopic examinations revealed no treatment-related abnormalities except for the treated skin. Microscopic examination of the treated skin revealed treatment-related changes including hyperplasia of the sebaceous glands, hyperplasia and hyperkeratosis in the epidermis, spongiosis in the epidermis, and multifocal vasculitis/perivasculitis in the dermis at all dose levels. **No adverse effects.** NOEL (M/F, systemic) = 1000 mg/kg/day based on no effects at the highest dose tested, NOEL (M/F, skin) < 150 mg/kg/day based on skin irritation. **Acceptable.** (Corlett, 5/10/01)